#14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent 4,587,258

Patentee: Gold et al.

Attn: Box Patent Ext.

Issue Date: May 6, 1986

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 37 CFR 1.710

March 26, 1991

Honorable Commissioner of
Patent and Trademarks
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is an application for extension of term of United States Patent 4,587,258 and a duplicate of the papers thereof, certified as such.

The contents of the application consist of APPOINTMENT OF AGENT duly signed by Schering Corporation (the record owner of the subject patent), POWER OF ATTORNEY duly signed by Hoechst Aktiengesellschaft (a licensee under said patent) and various statements made by the applicant and the undersigned attorney pursuant to 37 CFR 1.710 et seq. including EXHBITS A, B, C, D, E-1, E-2 and F.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or credit any overpayment to **Deposit Account No. 08-2445**. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Tatsuya Ikeda

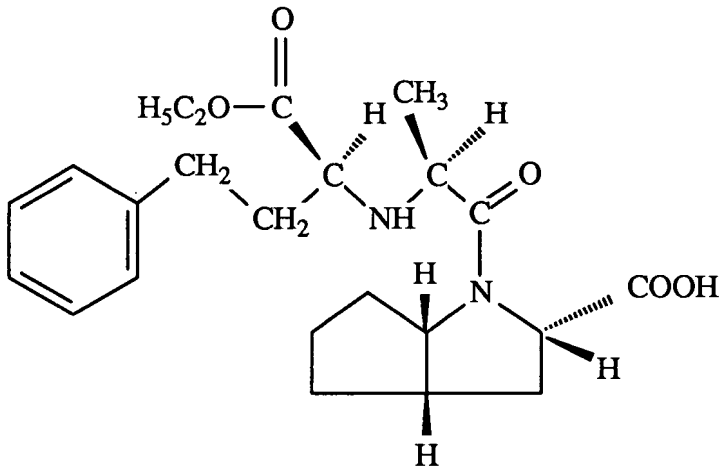
Tatsuya Ikeda
Attorney for Applicant
(Reg. No. 28,776)

Hoechst Celanese Corporation
Route 202-206
P.O. Box 2500
Somerville, New Jersey 08876-1258

(908) 231-3341
(March 26, 1991)

(1) **A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT:**

Approved product is Ramipril which can be named either cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl] octahydro-, [2S-[1[R*(R*)],2α,3aβ,6aβ]]-; or (2S,3aS,6aS)-1-[(S)-N-[(S)-1-carboxy-3-phenylpropyl]alanyl]octahydrocyclo-penta[b]pyrrole-2-carboxylic acid, 1-ethyl ester; and has the following chemical structure. (See USAN 1989, page 479).



Ramipril is the active ingredient of the new drug, Ramipril capsules, which has received FDA approval. Characteristics of said product may be seen from attached Exhibit A which is package insert prepared by Hoechst-Roussel Pharmaceuticals Incorporated, the sponsor of the approved NDA.

(2) **A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH THE REGULATORY REVIEW OCCURRED:**

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 USC 301 et seq.

(3) **AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE:**

Ramipril was approved by FDA for commercial marketing pursuant to Section 505 of FFDCA on January 28, 1991.

(4) **AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FEDERAL FOOD, DRUG AND COSMETIC ACT:**

The sole active ingredient of the approved new drug (which is a human drug) is Ramipril as identified above under Paragraph 1 and it has not previously been approved for commercial marketing or use under FFDCA.

(5) **A STATEMENT THAT THIS APPLICATION FOR PATENT TERM EXTENSION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD AND IDENTIFICATION OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:**

This application is expected to be hand-delivered to the United States Patent and Trademark Office on March 27, 1991 which is within the sixty day period starting from January 28, 1991 and ending on March 29, 1991.

(6) **A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT:**

A complete idenfication of the patent is presented as follows:

Names of the Inventors:	Elijah H. Gold; Bernard R. Neustadt; and Elizabeth M. Smith.
Patent Number:	4,587,258
Issue Date:	May 6, 1986
Date of Orignal Expiration:	May 6, 2003

(7) **A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT:**

A copy of said patent is attached hereto as Exhibit B.

(8) **A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION OCERTIFICATE ISSUED IN THE PATENT:**

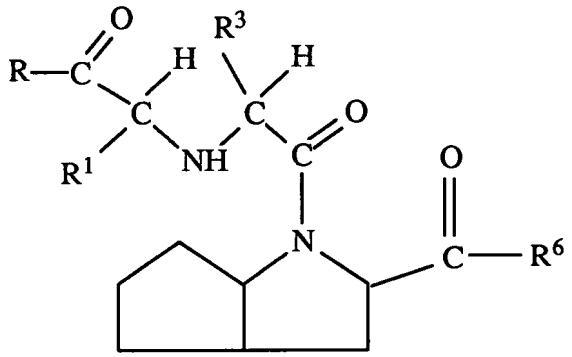
A copy of receipt of the first maintenance fee paid by Schering-Plough Corporation is attached hereto as Exhibit C. Said receipt has the mailing date of October 20, 1989.

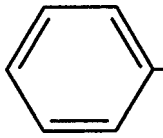
A copy of Statutory Disclaimer under 35 USC 253(a) filed by Schering Corporation on September 19, 1988 is attached hereto as Exhibit D. Said document disclaims Claims 3 through 6, inclusive, of said Gold et al patent.

Certificate of correction and re-examination certificate have never been issued.

(9) **A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT OR A METHOD OF USING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIMS AND DEMONSTRATES THE MANNER IN WHICH EACH APPLICABLE PATENT CLAIMS READS ON THE APPROVED PRODUCT OR A METHOD OF USING THE APPROVED PRODUCT:**

Claim 1 of said United States Patent 4,587,258 claims a compound represented by the formula



where the parameters R, R^1, R^3 and R^6 are as defined therein. Claim 1 reads on Ramipril when R is C_2H_5O; R^1 is  ; R^3 is CH_3; and R^6 is OH.

Claim 2 claims a compound according to Claim 1 which is a cis, endo isomer of octahydrocyclopenta[b]pyrrole-2(s)-carboxylic acid. Claim 2 reads directly on Ramipril. It is evident from the chemical structure presented under Paragraph 1 above that Ramiprl is a cis, endo isomer recited in Claim 2.

Claim 26 claims an antihypertensive composition comprising an effective amount of a compound as defined in Claim 1. Hence, Claim 26 reads on an antihypertensive composition comprising an effective amount of Ramipril when the parameters R, R^1, R^3 and R^6 meet the same limitations mentioned above in connection with Claim 1.

Claim 27 claims a method for reducing blood pressure in mammals which comprises administration of an effective amount of a compound as defined in Claim 1. Hence, Claim 27 reads on a method of using Ramipril for reducing blood pressure comprising administration of an effective amount of Ramipril when the parameters R, R^1, R^3 and R^6 meet the limitations mentioned above.

(10) **A STATEMENT OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 USC 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD:**

The Effective Date of the IND application: (30 days after the submission date)	January 27, 1984
The IND number:	IND 23,298
The Date on which the NDA was initially submitted:	November 2, 1988
The NDA number:	NDA 19-901
The Date on which the NDA was approved:	January 28, 1991

(11) **A BRIEF DESCRIPTION OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:**

By virtue of a license agreement between the record owner of the subject patent and Hoechst Aktiengesellschaft (Hoechst A.G.), the latter obtained certain rights under the subject patent. Hoechst-Roussel Pharmaceuticals Incorporated (HRPI) is an affiliate of Hoechst A.G. and is sublicensed by the latter to market the approved product in the United States. HRPI submitted an IND on December 28, 1983 (which became effective on January 27, 1984), and subsequently an NDA on November 2, 1988 and obtained approval of the NDA on January 28, 1991. The marketing applicant (HRPI) believes that it pursued its activities with due diligence throughout the regulatory review period, namely, the testing phase and the approval phase. Significant activities undertaken by HRPI during the regulatory review period are briefly described as EXHIBITS E-1 and E-2. The former relates to the testing phase, whereas the latter relates to the approval phase.

(12) **A STATEMENT THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:**

Applicant believes that the subject patent is eligible for patent term extension pursuant to 35 USC 156(a) for the following reasons:

(1) The term of the patent has not expired before this application is being submitted.

(2) The term of the patent has never been extended.

(3) This application for patent term extension is submitted by an authorized agent of the record owner of the subject patent.

(4) The product has been subject to a regulatory review period before its commercial marketing or use as evident from Paragraph 11 above.

(5) The permission for the commercial marketing or use of the product after said regulatory review period is the first commercial marketing or use of the product under the provision of FFDCA.

Applicant believes that the subject patent is entitled to 632 days of term extension. This length of extension has been calculated as follows. Details of the key days are presented as EXHIBIT F.

(1) Number of days of the testing phase which is subsequent to the patent issue date is 910 days (between 5/06/86 and 11/02/88);

(2) Number of days of the approval phase subsequent to the patent issue date is 817 days (between 11/02/88 and 1/28/91);

The sponsor of the subject IND and NDA acted in due diligence throughout the testing and the approval phases as evident from the aforementioned EXHIBITS E-1 and E-2;

(3) One half of the testing period (subsequent to the patent issue date and supported by due diligence) is 455 days;

(4) The sum of the period recited under Paragraph 3 and the period recited under Paragraph 2 is 1272 days (modified regulatory review period);

(5) The subject patent issued subsequent to September 24, 1984 (Effective Date of the 1984 Waxman-Hatch Act);

(6) The date of approval of the subject NDA is January 28, 1991;

(7) The original expiration date of the subject patent is May 6, 2003;

(8) Addition of the modified regulatory review period of 1,272 days recited under Paragraph 4 **would** extend the expiration date of the subject patent to October 20, 2006;

(9) However, the extension period is subject to the five year limitation under 35 USC 156(g)(6)(A); and hence, the subject patent can not be extended beyond May 6, 2008;

(10) The patent term extension is also subject, under 35 USC 156(c)(3), to the fourteen year limitation as to the net effective life of the patent after the NDA approval. This limitation dictates that the subject patent can not be extended beyond January 28, 2005;

(11) In light of the conclusions stated under Paragraphs 8, 9 and 10, the controlling limitation is the fourteen year limitation recited under Paragraph 10. Thus, the extended expiration date of the subject patent is believed to be January 28, 2005, namely, fourteen years after the date of approval of the subject NDA. Thus, the net extension period of the subject patent is believed to be 632 days (from May 6, 2003 to January 28, 2005).

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health Services under 37 CFR 1.765 any information which is material to the determination of entitlement to the extension sought herein.

(14) **THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION:**

Please charge the Deposit Account Number 08-2445 (of Hoechst-Celanese Corporation) in the amount of **$600.00** as the fee covering the instant application for patent term extension. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. **08-2445**.

(15) **THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:**

Please forward all inquiries and correspondence relating to this application for patent term extension to:

Tatsuya Ikeda
Patent Department
Hoechst Celanese Corporation
P.O. Box 2500
Route #202-206 North
Somerville, New Jersey 08876-1258
Telephone #: (908) 231-3341

(16) **A DUPLICATE OF THE APPLICATION PAPERS, CERTIFIED AS SUCH:**

A duplicate of this application papers, certified as such, is enclosed herewith.

(17) **DECLARATION OF ATTORNEY:**

I hereby declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application; that I am a patent attorney authorized to practice before the United States Patent and Trademark Office; that as evident from the enclosed APPOINTMENT OF AGENT duly signed by an officer of Schering Corporation, Hoechst Aktiengesellschaft has been granted certain rights under the subject patent; that Hoechst-Roussel Pharmaceuticals Incorporated, namely, the sponsor of the subject IND and NDA, is an affiliate of Hoechst Aktiengesellschaft and is sublicensed by Hoechst Aktiengesellschaft to market the approved product in the United States; that by a virtue of said APPOINTMENT OF AGENT, Hoechst Aktiengesellschaft and its designee are authorized to act on behalf of Schering Corporation in this application; that by virtue of the enclosed POWER OF ATTORNEY duly signed by Hoechst Aktiengesellschaft, I am the authorized designee of Hoechst Aktiengesellschaft for the purpose of submitting this application for patent term extension, and hence, have the authority to submit and prosecute this application on behalf of Schering Corporation; that I have reviewed and understand the contents of this application being submitted; that I believe the subject patent is subject to extension pursuant to 37 CFR 1.710; that I believe an extension of the length

claimed is justified under 35 USC 156 and the applicable regulations; and that I believe that the subject patent meets the conditions for term extension as set forth in 37 CFR 1.720.

Respectfully submitted,

Tatsuya Ikeda

Tatsuya Ikeda
Attorney for Applicant(s)
(Reg. No. 28,776)

Hoechst Celanese Corporation
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(908) 231-3341

APPOINTMENT OF AGENT

WHEREAS Schering Corporation, (hereinafter "Schering") having its principal office at 2000 Galloping Hill Road Kenilworth, New Jersey is the owner of record of U.S. Patent No. 4,587,258 entitled Angiotensin-Converting Enzyme Inhibitors which was granted May 6, 1986 by virtue of an assignment of such patent to Schering recorded September 20, 1984, Reel 4300, Frames 0782-3;

WHEREAS Hoechst Aktiengesellschaft (hereinafter "Hoechst") entered into a license agreement with Schering underwhich Hoechst was granted certain rights under U.S. Patent No. 4,587,258;

WHEREAS Hoechst is desirous of marketing a compound within the scope of the claims of U.S. Patent No. 4,587,258 including a compound known generically as Ramipril;

WHEREAS Hoechst received marketing approval on January 28, 1991 from the United States Food and Drug Administration to market Ramipril;

WHEREAS 35 U.S.C. Section 156, known as the Drug Price Competition and Patent Term Restoration Act of 1984, provides at (a)(3) that an application for an extension of a patent term can be submitted by the owner of record of the patent or its agent;

NOW, THEREFORE, Schering Corporation hereby appoints Hoechst Aktiengesellschaft, its subsidiaries and its and/or its designees as Schering's agents for the express purpose of submitting the application for patent term extension for U.S. Patent No. 4,587,258 covering Ramipril under 35 USC 156. This appointment shall be co-extensive with the term of the underlying license agreement.

SCHERING CORPORATION

By: _____
John T. Fogarty

Date: March 11, 1991

Title: Vice President

P/ADAG4709

POWER OF ATTORNEY

WHEREAS, Hoechst Aktiengesellschaft (hereinafter "Hoechst") having its principal place of business at 6230 Frankfurt am Main 80, Federal Republic of Germany, has entered into a license agreement with Schering Corporation (hereinafter "Schering") having its principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey, and by virtue thereof has been granted certain rights under Gold et al., U.S. Patent No. 4,587,258 covering a compound known generically as Ramipril;

WHEREAS, Hoechst and its affiliates are desirous of marketing a compound within the scope of the claims of U.S. Patent No. 4,587,258 including a compound known generically as Ramipril;

WHEREAS, Hoechst-Roussel Pharmaceuticals Incorporated (which is an affiliate of Hoechst) has received marketing approval on January 28, 1991 from the United States Food and Drug Administration to market Ramipril;

WHEREAS, 35 U.S.C. Section 156, known as the Drug Price Competition and Patent Term Restoration Act of 1984, provides at (a) (3) that an application for an extension of a patent term can be submitted by the owner of record of the patent or its agent;

WHEREAS, by virtue of APPOINTMENT OF AGENT signed by Schering and dated March 11, 1991, Hoechst is authorized to designate a person as a Schering agent for the express purpose of submitting an application for patent term extension of said U.S. Patent No. 4,587,258;

NOW, THEREFORE, Hoechst hereby designates Dr. Tatsuya Ikeda (Reg. No. 28,776) who is an employee of Hoechst Celanese Corporation and serves Hoechst-Roussel Pharmaceuticals Incorporated in intellectual property matters, as an authorized attorney for submitting and prosecuting said application for patent term extension.

HOECHST AKTIENGESELLSCHAFT

By: _____

Prokurist

By: _____

Authorized Signatory

EXHIBIT A

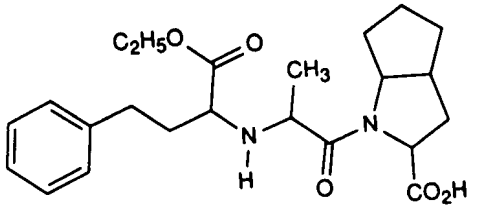
710300-2/91

ALTACE™ (ramipril)*

DESCRIPTION

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105°C and 112°C.

Ramipril's chemical name is (2*S*,3a*S*,6a*S*)-1[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl]alanyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid, 1-ethyl ester; its structural formula is:



Its empiric formula is $C_{23}H_{32}N_2O_5$, and its molecular weight is 416.5.

Ramiprilat, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group.

ALTACE™ (ramipril) is supplied as hard shell capsules containing 1.25 mg, 2.5 mg, 5 mg, and 10 mg of ramipril. The inactive ingredients present are pregelatinized starch NF, gelatin, and titanium dioxide. The 1.25 mg capsule shell contains yellow iron oxide, the 2.5 mg capsule shell contains D&C yellow #10 and FD&C red #40, the 5 mg capsule shell contains FD&C blue #1 and FD&C red #40, and the 10 mg capsule shell contains FD&C blue #1.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with ALTACE alone for up to 56 weeks, approximately 4 percent of patients during the trial had an abnormally high serum potassium and an increase from baseline greater than 0.75 mEq/L, and none of the patients had an abnormally low potassium and a decrease from baseline greater than 0.75 mEq/L. In the same study, approximately 2% of patients treated with ALTACE and hydrochlorothiazide for up to 56 weeks had abnormally high potassium values and an increase from baseline of 0.75 mEq/L or greater, and approximately 2 % had abnormally low values and decreases from baseline of 0.75 mEq/L or greater. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ALTACE remains to be elucidated.

While the mechanism through which ALTACE lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ALTACE has an antihypertensive effect even in patients with low-renin hypertension. Although ALTACE was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-black patients.

PHARMACOKINETICS AND METABOLISM

Following oral administration of ALTACE, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced.

Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%; *in vitro*, these percentages are independent of concentration over the range of 0.01 to 10μg/ml.

Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive.

After oral administration of ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine, and about 40% is found in the feces. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the 2.5-20 mg dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline, which represents distribution of the drug into a large peripheral compartment and subsequent binding to both plasma and tissue ACE, has a half-life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of 9-18 hours. The terminal elimination phase has a prolonged half-life (>50 hours) and probably represents the binding/dissociation kinetics of the ramiprilat/ACE complex. It does not contribute to the accumulation of the drug. After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations within the therapeutic range was 13-17 hours.

After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of ALTACE, especially at low doses (2.5 mg), but the difference is clinically insignificant.

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. Compared to normal subjects, patients with creatinine clearance less than 40 ml/min/1.73m^2 had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations. (See DOSAGE AND ADMINISTRATION.)

In patients with impaired liver function, the metabolism of ramipril to ramiprilat appears to be slowed, possibly because of diminished activity of hepatic esterases, and plasma ramipril levels in these patients are increased about 3-fold. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function, and the effect of a given dose on plasma ACE activity does not vary with hepatic function.

PHARMACODYNAMICS

Single doses of ramipril of 2.5-20 mg produce approximately 60-80% inhibition of ACE activity 4 hours after dosing with approximately 40-60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 mg or more cause plasma ACE activity to fall by more than 90% 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small multiple doses presumably reflects saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

Administration of ALTACE to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See WARNINGS.) Use of ALTACE in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone.

In single-dose studies, doses of 5-20 mg of ALTACE lowered blood pressure within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (4-12 weeks) controlled studies, once-daily doses of 2.5-10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mm Hg more than placebo. In comparisons of peak vs trough effect, the trough effect represented about 50-60% of the peak response. In a titration study comparing divided (bid) vs qd treatment, the divided regimen was superior, indicating that for some patients the antihypertensive effect with once-daily dosing is not adequately maintained. (See DOSAGE AND ADMINISTRATION.)

In most trials, the antihypertensive effect of ALTACE increased during the first several weeks of repeated measurements. The antihypertensive effect of ALTACE has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of ALTACE has not resulted in a rapid increase in blood pressure.

ALTACE has been compared with other ACE inhibitors, beta-blockers, and thiazide diuretics. It was approximately as effective as other ACE inhibitors and as atenolol. In both Caucasians and blacks, hydrochlorothiazide (25 or 50 mg) was significantly more effective than ramipril.

Except for thiazides, no formal interaction studies of ramipril with other antihypertensive agents have been carried out. Limited experience in controlled and uncontrolled trials combining ramipril with a calcium channel blocker, a loop diuretic, or triple therapy (beta-blocker, vasodilator, and a diuretic) indicate no unusual drug-drug interactions. Other ACE inhibitors have had less than additive effects with beta adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

ALTACE was less effective in blacks than in Caucasins. The effectiveness of ALTACE was not influenced by age, sex, or weight.

In a baseline controlled study of 10 patients with mild essential hypertension, blood pressure reduction was accompanied by a 15% increase in renal blood flow. In healthy volunteers, glomerular filtration rate was unchanged.

INDICATIONS AND USAGE

ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS

ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with history of angioneurotic edema.

WARNINGS

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension

ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patents, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased. If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of neonatal hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial malformations, hypoplastic lung development, and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hypokalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Ramipril could theoretically be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

Ramipril has been shown to increase the incidence of dilated renal pelvises in rat fetuses, to retard birth weights in mice, and to be toxic to pregnant rabbits and pregnant cynomolgus monkeys, but not, in any of these studies, to produce terata or to affect fertility, reproductive performance, or pregnancy. On a mg/kg basis, the doses used in these studies were 125-2500 times (in rats), 2500 times (in mice), more than 12 times (in monkeys), and more than twice (in rabbits) the maximum recommended human dose.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See DRUG INTERACTIONS.)

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE™ (ramipril) should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions

With diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced. (See DOSAGE AND ADMINISTRATION.)

With potassium supplements and potassium-sparing diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, or antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1,000 mg/kg/day for 18 months). Dosages greatly in excess of those recommended for humans produced hypertrophy of the renal juxtaglomerular apparatus in mice, rats, dogs, and monkeys. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy

Pregnancy Category D: See WARNINGS.

Nursing Mothers

Ingestion of a single 10 mg oral dose of ALTACE resulted in undetecttable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Geriatric Use

Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below.

PATIENTS IN US PLACEBO CONTROLLED STUDIES

	Altace (N=651)		Placebo (N=286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (In some, a causal relationship to drug use is uncertain.):

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see PRECAUTIONS and WARNINGS), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, and myocardial infarction.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment.

Gastrointestinal: Abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritis, or rash, with or without fever), photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings:

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See PRECAUTIONS and WARNINGS.)

Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See PRECAUTIONS and WARNINGS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities: all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE

The oral LD_{50} of rats and mice is 10-11 g/kg. In dogs, oral doses as high as 1 g/kg induced only mild gastrointestinal distress. Human overdoses of ramipril have not been reported, but the most common manifestation of human ramipril overdosage is likely to be hypotension.

Laboratory determinations of serum levels of ramipril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of ramipril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of ramipril and its metabolites. Similarly, it is not known which, if any, of these substances can be usefully removed from the body by hemodialysis.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of ramipril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic can be added.

Concomitant administration of ALTACE with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. (See PRECAUTIONS.)

In patients who are currently being treated with a diuretic, symptomatic hypotension occaisionally can occur following the initial dose of ALTACE. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with ALTACE (see WARNINGS). Then, if blood pressure is not controlled with ALTACE alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used to avoid excess hypotension.

DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT: For patients with a creatinine clearance <40 ml/min/1.73m^2 (serum creatinine >2.5 mg/dl), the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg.

HOW SUPPLIED

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in hard gelatin capsules, packaged in bottles of 100 capsules. ALTACE is also supplied in blister packages (10 capsules/blister card).

ALTACE capsules are supplied as follows:

1.25 mg—yellow capsule
NDC 0039-0103-10—bottles of 100
NDC 0039-0103-11—Unit Dose Cartons of 100

2.5 mg—orange capsule
NDC 0039-0104-10—bottles of 100
NDC 0039-0104-11—Unit Dose Cartons of 100

5 mg—red capsule
NDC 0039-0105-10—bottles of 100
NDC 0039-0105-11—Unit Dose Cartons of 100

10 mg—Process Blue capsules
NDC 0039-0106-10—bottles of 100

Dispense in well-closed container with safety closure.
Store at controlled room temperature (59 to 86° F).
Caution: Federal law prohibits dispensing without prescription.
Altace TM HOECHST AG
*US Patent 4,587,258
Made in USA

710300-2/91

HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

EXHIBIT B

United States Patent [19]

Gold et al.

[11] **Patent Number: 4,587,258**

[45] **Date of Patent: May 6, 1986**

[54] **ANGIOTENSIN-CONVERTING ENZYME INHIBITORS**

[75] Inventors: **Elijah H. Gold; Bernard R. Neustadt,** both of West Orange; **Elizabeth M. Smith,** Verona, all of N.J.

[73] Assignee: **Schering Corporation,** Kenilworth, N.J.

[21] Appl. No.: **635,390**

[22] Filed: **Jul. 30, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 258,484, Apr. 28, 1981, which is a continuation-in-part of Ser. No. 201,649, Oct. 28, 1980, abandoned, which is a continuation-in-part of Ser. No. 199,886, Oct. 23, 1980, abandoned.

[30] **Foreign Application Priority Data**

Oct. 15, 1981 [EP] European Pat. Off. 81108348.4

[51] **Int. Cl.**[4] **A61K 31/40;** C07K 5/06; C07D 209/02

[52] **U.S. Cl.** **514/412;** 514/414; 548/452

[58] **Field of Search** ..... 548/515, 452; 260/112.5 R; 514/412, 414

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,344,949	8/1982	Hoefle et al.	424/258
4,404,206	9/1983	Vincent et al.	424/258

Primary Examiner—Delbert R. Phillips
Attorney, Agent, or Firm—Anita W. Magatti; Stephen I. Miller; Gerald S. Rosen

[57] **ABSTRACT**

Novel compounds with angiotensin-converting enzyme inhibitory activity are disclosed. Such compounds are useful in the treatment of cardiovascular disorders, especially hypertension and congestive heart failure, and are useful in the treatment of glaucoma.

30 Claims, No Drawings

Disclaimer

4,587,258.—*Elijah H. Gold*; *Bernard R. Neustadt*, both of West Orange; *Elizabeth M Smith*, Verona, all of N.J. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. Patent dated May 6, 1986. Disclaimer filed Sept. 30, 1988, by the assignee, *Schering Corp.*

Hereby enters this disclaimer to claims 3-6 of said patent.

[*Official Gazette March 7, 1989.*]

EXHIBIT C

Case 2328US
Oct. 5, 1989

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

ANITA W. MAGATTI
SCHERING-PLOUGH CORPORATION
1 GIRALDA FARMS, MADISON, NJ 07940

DATE MAILED
10/20/89

083193

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,587,258	173	490	----	06/635,390	05/06/86	07/30/84	04	ND	PAID

2328 US

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	2328

DIRECT THE RESPONSE TOGETHER WITH PART B OF THIS NOTICE, AND ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

EXHIBIT D

Express Mail B No.: 71379008

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

INVENTORS	:	ELIJAH H. GOLD, et al.
PATENT NO.	:	4,587,258
GRANTED	:	MAY 6, 1986
APPLICATION SERIAL NO.	:	635,930
FILED	:	JULY 30, 1984
FOR	:	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

STATUTORY DISCLAIMER UNDER
35 U.S.C. SECTION 253(a)

S I R :

Schering Corporation, a corporation of New Jersey, having an office at Galloping Hill Road, Kenilworth, N.J. 07033, which represents that it is the owner of the entire right, title and interest, by reason of an assignment recorded as of September 20, 1984, at reel 4300, frames 782-3, of the above-identified patent application Serial No. 635,390, filed July 30, 1984, of Letters Patent No. 4,587,258 granted to it hereby disclaims claims Nos. 3 through 6, inclusive, of said patent.

Authorization to charge the $56.00 fee required by 37 C.F.R. 1.20(d) to Deposit Account 19-0365 is hereby granted. This paper is submitted in duplicate.

Signed at Madison, New Jersey, this 19th day of September, 1988.

Schering Corporation

By _____
David J. Mugford
Assistant Secretary
Schering Corporation

DATE	TO/FROM	SUBJECT
12/28/83	FDA/H-RPI	Submission of original IND. (Caps 1, 2, 4 mg placebo
1/23/84	FDA/H-RPI	Telecon between L. Baum and J. Knight re: status of IND. #23,298 assigned as well as the following reviewers: Martin Rose, M.D. - Medical Reviewer, Stuart Zimmerman - Chemist and Gordon Johnson - Pharmacologist.
1/20/84	H-RPI/FDA	Acknowledgement of receipt of our IND Submission, dated December 28, 1983 and assigned IND #23,298.
2/3/84	H-RPI/FDA	Telecon between Dr. Rose of the C-R Division and Drs. Lassman, Affrime and D. Bucceri requesting changes in Protocol 101.
2/23/84	FDA/H-RPI	Amendment to Sections 9 and 10 of IND. Changes incorporated into Protocol 102 which replaces Protocol 101.
2/23/84	FDA/H-RPI	Meeting at FDA between DJB and Ms. Knight re: changes made in Protocol 102 and her help in expediting Dr. Rose's review.
2/29/84	FDA/H-RPI	Telecon between Dr. Rose and L. Baum 2/23/84 amendment to our IND - Protocol 102.
3/15/84	FDA/H-RPI	Amend Sections 9 & 10 of IND to add Dr. W. Flanigan as an investigator under Protocol 102.
3/14/84	FDA/H-RPI	Telecon between Dr. Lassman, L. Baum, D. Bucceri and Dr. Rose of the Cardio-Renal Division re: Protocol 102.
3/14/84	H-RPI/FDA	Telecon between Dr. Rose and D. Bucceri the multi-center study conducted in Protocol 102.
3/21/84	H-RPI/FDA	Telecon between Ms. Knight and L. Baum re: Assignment of 1C classification by Dr. Lipicky to HOE 498
6/26/84	FDA/H-RPI	Amend IND to provide information for 5 mg and 10 mg capsules.
10/19/84	FDA/H-RPI	Submit Amendment II to Protocol 102 to provide 1 mg and 20 mg doses and revised investigator's brochure.
12/14/84	FDA/H-RPI	Amend IND for Dr. Lasseter to continue Protocol 102 study with Amendment II (1 mg & 20 mg).
1/15/84	FDA/H-RPI	First Annual Progress Report - Section 5: Methods, Facilities & Controls, Section 6a: Preclinical Investigations, Section 6b: Clinical Investigations & Section 10: Outline of Investigations.
3/21/85	FDA/H-RPI	IND amendment for Sections 2, 3, 5, 7, 9 & 10 - Protocol 102 report and Amendment 3; Protocols 250 & 253.

Date of Message	TO/FROM	Subject
09/14/90	FDA/HRPI	trough levels of ramiprilat with QD vs BID dosing.
09/17/90	FDA/HRPI	Article containing binding data for ramipril & ramirilat.
09/18/90	FDA/HRPI	Foreign Case No. 90 0395 T01M (follow-up).
09/19/90	HRPI/FDA	Telecon: Dr. Teng/H. Lassman to request computer-simulated data on 20 mg QD & 10 mg BID at steady state.
09/21/90	FDA/HRPI	Telecon: Dr. Fenichel/M. Gordon re: status of SBA review--should have his comments by week end. He requests we make recommended changes & return within 1 wk. To approve by year end, must be to Temple by end of Oct.
10/01/90	FDA/HRPI	Fax of results of computer simulation on 20 mg QD & 10 mg BID dosing to Dr. Teng from H. Lassman.
10/03/90	FDA/HRPI	Telecon: Dr. Fenichel/M. Gordon, J. Hubbard, D. Costello re: SBA.
10/03/90	FDA/HRPI	Translations from STudy HOE 498/1/D/114 and Computer Simulation.
10/04/90	FDA/HRPI	NDA Amendment - Final Reports of Toxicology Studies.
10/10/90	FDA/HRPI	Teleconference: L. Pavloff, M. Bloomstein, B. Bollwage/S. Zimmerman to discuss our desire to use a single-color capsule to re- place bi-color capsule currently described in our NDA.
10/11/90	HRPI/FDA	Telecon: Dr. Resnick/D. Bucceri to ask if same pathologist had read slides from which were reported the lymphomas/malignant lym- phomas.
10/16/90	FDA/HRPI	NDA Amendment - C/M/C.
10/18/90	FDA/HRPI	Telecon: B. Bollwage/S. Zimmerman to inform him of the materials in our C/M/C amendment in addition to the capsule color change.
10/18/90	FDA/HRPI	Telecon: M. Gordon/Dr. Fenichel re: review of all sections of SBA including PI. He expects to return it to us for corrections by the end of the week.
10/19/90	FDA/HRPI	Second draft of the safety section of the

HOE 498

Date	To/From	Subject
5/3/85	FDA/H-RPI	Amend Sections 9 and 10 of IND - Protocol 250.
5/22/85	FDA/H-RPI	Amend Section 9 to add Drs. Boyles & Strauss.
6/19/85	FDA/H-RPI	Amend Section 9 - Protocols 250 and 253.
6/17/85	FDA/H-RPI	Amend Sections 9 & 10 to add W. Garland, MD, M. Korc, MD and J. Kostis/Protocol 250; L. Smith, MD and R. Williams, MD/Protocol 253.
7/25/85	FDA/H-RPI	Amend Section 6a of IND to add six month rat and dog studies.
8/7/85	FDA/H-RPI	Amend Section 9 of IND, change of address Protocol 250
10/7/85	FDA/H-RPI	Amend IND jSections 9 & 10. Add invest to Protocols 250 and 253 and Amendments 253.1 and 253.2.
11/26/85	FDA/H-RPI	Amend Sections 3-5 for HCTZ 25 and 50 mg; Sections 9 & 10 to add co-investigators and Amendments 250.1 and 250.2 to Protocol 250.
1/7/86	FDA/H-RPI	Second Annual Progress Report - Section 5: Methods, Facilities & Controls; Section 6a: Preclinical Investigations; Section 6b: Clinical Investigations; Section 10: Outline of Investigations; Section 16: GLP Compliance Statement.
1/14/86	FDA/H-RPI	Amend IND Section 10 to add Protocol Amendment 253.3 (one year open-label extension).
1/23/86	FDA/H-RPI	Amend Sections 9 & 10 to add Dr. Benotti - Protocol 201.
2/5/86	FDA/H-RPI	Amend Sections 9 and 10 to add Davidson, Kann, Levy, Mroczek, Nedelman, Reeves, Silberman, Sonnenblick and Spinowitz and Protocol 254.
3/11/86	FDA/H-RPI	Amend Section 9 to add D. McCarron, MD and J. Markis,M Michael Ryan, MD (do-investigator).
3/18/86	FDA/H-RPI	Submit a report pertaining to the quality control observation of degradation of HOE 498.
4/9/86	FDA/H-RPI	Amendment to Section 9: add C. Bunde, MD & R. McMaster MD and delete E. Buchman, MD as co-investigator under Dr. Gourzis for Protocol 254.
4/11/86	H-RPI/FDA	Request for response to M/C questions prior to beginning Phase III investigations.
4/22/86	FDA/H-RPI	15-day alert: Project: 179, Protocol: SWE, Inv. 001, Patient: 0006.
5/28/86	FDA/H-RPI	Amend Section 9: J. Herron, MD (Protocol 107) and B. Levy, MD (add co-investigator) (Protocol 254).
5/29/86	FDA/H-RPI	Amend Section 3-5 for Maalox suspension & Section 9 & 10: Jerry M. Herron, MD; Protocol 108.

Date of Message	TO/FROM	Subject
	FDA/HRPI	DER No. U860578.
01/07/86	FDA/H-RPI	2nd Annual Progress Rpt.- Sec. 5: Methods, Facilities & Controls; Sec. 6A: Preclinical Investigations; Sec. 6b: Clinical Investigations; Sec. 10: Outline of Investigations; Sec. 16: GLP Compliance Statement
01/14/86	FDA/H-RPI	Amend IND Section 10 to add Protocol Amendment 253.3 (one year open-label extension).
01/23/86	FDA/H-RPI	Amend Sections 9 & 10 to add Dr. Benotti - Protocol 201.
02/05/86	FDA/H-RPI	Amend Sections 9 & 10 to add Davidson, Kann, Levy, Mroczek, Nedelman, Reeves, Silberman, Sonnenblick and Spinowitz and Protocol 254.
03/11/86	FDA/H-RPI	Amend Section 9 to add D. McCarron, MD and J. Markis, MD, Michael Ryan, MD (co-investigator).
03/18/86	FDA/H-RPI	Submit a report pertaining to the quality control observation of degradation of HOE 498.
04/09/86	FDA/H-RPI	Amendment to Section 9: add C. Bunde, MD & R. McMaster, MD and delete E. Buchman, MD as co-investigator under Dr. Gourzis for Protocol 254.
04/11/86	H-RPI/FDA	Request for response to M/C questions prior to beginning Phase III investigations.
04/22/86	FDA/H-RPI	15-day alert: Project: 179, Protocol: SWE, Inv. 001, Patient: 0006.
05/28/86	FDA/H-RPI	Amend Sect. 9: J. Herron, MD (Protocol 107) and B. Levy, MD (add co-investigator) (Protocol 254).
05/29/86	FDA/H-RPI	Amend Section 3-5 for Maalox suspension & Section 9 & 10: Jerry M. Herron, MD; Protocol 108.
05/29/86	FDA/H-RPI	Amend Section 9: Study site address change for Dr. Lewis for Protocol 253.
06/27/86	FDA/HRPI	Amend Section 10: ProtocoL 201A
07/03/86	FDA/HRPI	Amend Sections 2-5: hydrochlorothiazide 25mg and Section 10: Protocol 351.
07/14/86	FDA/HRPI	Project 179, Protocol 201, Investigator 8NL,

Date of Message	TO/FROM	Subject
07/14/86	FDA/HRPI	Patients 0005 and Second Patient.
07/24/86	FDA/HRPI	Amend Section 9: Drs. Singh & Papademetriou added under Protocol 201.
08/01/86	HRPI/FDA	Amend Section 9: Dr. Liang under Protocol 201, Dr. Woehler; Protocol 254.
08/05/86	HRPI/FDA	Response to questions in FDA letter of 4/11/86 re: Manufacturing/Controls and Biopharmaceutics.
08/22/86	HRPI/FDA	Amend Section 9: Dr. Blum under Protocol 351.
08/25/86	FDA/HRPI	Patient No. 0010 - Protocol 201.
09/03/86	HRPI/FDA	Amend Section 9: New study sites under Protocol 254 - Spinowitz' group.
09/08/86	HRPI/FDA	Addition of Investigators, Strauss - 350, Lewis - 350, Davidov - 351. Submission of Protocol 350.
09/15/86	FDA/H-RPI	Section 9: Addition of investigators Conrad (Protocol 351) and Goldstein (Protocol 350).
09/24/86	FDA/HRPI	Addition of investigators under Protocols 254, 350 and 351.
09/26/86	FDA/HRPI	Addition of Investigators Bowman, Lucas, Morledge, Roebuck, Frazer and Pleskow under Protocol 350 and 351.
10/10/86	FDA/HRPI	Amendment to Section 9: Add investigators Knapp/Lanies (Protocol 350); Ferraro (Protocol 351); Miller (Protocol 350); Pappas (Protocol 351); Angelo (Protocol 351).
10/14/86	FDA/HRPI	IND Amendment; Addition of investigators Weidler (350) and Maskin (201).
10/24/86	FDA/HRPI	Amend Sec. 9: Add Inv., Drs. Kaloyanides, Gilderman, Katz Chardo, & co-inv. Drs. Dix, Schulman, Graber, Temkin, Steinberg, Rudolph Brachfeld, Petroski, Swietnicki, Kaufman, Goldstein & Ginsberg to Protocol 351.
10/29/86	FDA/HRPI	Amend Sec. 9: Addition of Investigators & Co-Investigators under Protocols 350 & 351.
10/31/86	FDA/HRPI	15-Day Alert Report: Project 179, Protocol 253, Investigator 021, Patient 0715.
11/05/86	FDA/HRPI	Amend Sec. 9: Addition of Inv. Schlamowitz,

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11/05/86	FDA/HRPI	Rofman, Vergis & Schnaper & Co-Inv. to Protocols 350 & 250.2. Sec. 10: Submitted an amendment to Protocol 250.
11/10/86	FDA/HRPI	Amend Sec. 9: Addition of Investigators & Co-investigators to Protocol 352; Sec. 10: Protocol 352 is attached.
11/14/86	FDA/HRPI	Amend Sec. 9: Additon of Investigators & Co-Investigators to Protocols 350 and 352.
11/25/86	FDA/HRPI	15-Day Alert: Project 179, Protocol 201, Investigator 048, Patient 0002.
11/26/86	FDA/HRPI	Amend Sec. 9: Addition of Investigators and Co-investigators to Protocol 352.
12/01/86	FDA/HRPI	15-Day Alert: Project 179, Protocol 304, Investigator D05, Patient HI01.
12/02/86	FDA/HRPI	15-Day Alert: Project 179, Protocol 203, Investigator GRB, Patient HI01.
12/16/86	FDA/HRPI	Third Ann. Prog. Rep.- Sec. 6: Methods, Facilities & Controls; Sec. 6a: Preclinical Investigations; Sec. 6b: Clinical Investigations; Sec. 10: Outline of Investigations; Sec. 16: GLP Statement
12/18/86	FDA/HRPI	Amend Sec. 9 to add Investigators and Co-Investigators to Protocols 351 & 352.
12/30/86	FDA/HRPI	IND Initial Report. Project: 179, Protocol: 351. Investigator 011 & Patient 0606. Investigator 051 & 0404.
01/07/87	FDA/HRPI	IND Initial Report. Project 179, Prot. 600, Inv. FCT, Patient 0007.
01/08/87	FDA/HRPI	IND Initial Report. Project 179, Prot. 253, Inv. 026, Patient 0522.
01/09/87	FDA/HRPI	Amend Sections 9 & 10 to Protocol Amendment 253.4 and 250.3 (attached).
01/27/87	FDA/HRPI	IND Initial Report. Project 179, Protocol 600, Investigator: FCT, Patient 0008.
01/28/87	FDA/HRPI	Amend Section 9 to add Investigator N. J. Canzallo, MD & co-investigatot N. Madias, MD to Protocol 352.
02/10/87	FDA/HRPI	Amend Sec. 9 to add co-investigators J. Seltzer, MD & D. Hensleigh, MD to the

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02/10/87	FDA/HRPI	ongoing trials to Protocol 352.
02/10/87	FDA/HRPI	Report: Project 179, Protocol 600, Inv. FCT, Patient 0011.
02/13/87	FDA/HRPI	Amend Sec. 9 to add co-investigator S. G. Hoffman, D.O. to the ongoing trial to Protocol 351.
02/19/87	FDA/HRPI	Amend Sec. 9 to add T. Kotchen, MD as investigator and G. Guthrie, Jr., MD as co-investigator to Protocol 351.
03/09/87	FDA/HRPI	IND Initial Report. Project 179, Category 600, Investigator FCT, Patient 0012.
03/09/87	FDA/HRPI	IND Follow Up Report. Project 179, Protocol 351, Investigator 065, Patient 0606.
03/10/87	FDA/HRPI	Amend Sections 2-5, 9 & 10 to Protocol 354.
03/16/87	FDA/HRPI	Amend Sec. 9 to Protocol 354.
03/25/87	FDA/HRPI	Submit final report of Phase I clinical investigation (Protocol 102)j.
03/30/87	FDA/HRPI	Amend Section 9 to Protocol 354.
03/30/87	FDA/HRPI	Amend Section 9 to Protocols 354 and 352.
03/31/87	FDA/HRPI	IND Follow-up Report. Project 179, Category 600, Investigator FCT, Patient 0012.
03/31/87	FDA/HRPI	IND Initial Report. Project 179, Category 600, Investigator FCT, Patient 0013.
03/31/87	FDA/HRPI	IND Initial Report. Project 179, Category 600, Investigator FCT, Patient 0014.
04/10/87	FDA/HRPI	Literature Report No. 160001.
04/14/87	FDA/HRPI	Amend Section 9 to Protocols 354 & 352.
04/20/87	FDA/HRPI	Amend Section 9 to add Investigator W. Miller, MD to Protocol 354.
04/23/87	FDA/HRPI	Submitting a revised signed 1573 for Investigator R. Brobyn, MD & Co-Investigator J. Baker, MD to Protocol 352.
04/23/87	FDA/HRPI	Amend Section 9 to add Inv. W. Mroczek, MD & Co-Inv. K. Allenby, MD, J. Burris, MD, R. Mills, MD, V. Papademetriou, MD & E. Sethi, MD to Protocol 354

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05/01/87	FDA/HRPI	Amend Sections 9 & 10 to Protocol 201, 352 & Amendment 354.1 (attached).
05/11/87	FDA/HRPI	IND Safety Report. Project 179, Category 600, Inv. FCT, Patient 0017.
05/14/87	FDA/HRPI	IND Safety Report. Project 179, Category 600, Inv. FCT, Patient 0018f
05/26/87	FDA/HRPI	Information Amendment: Toxicology Report - 24-month Rat Carcinogenicity.
05/27/87	FDA/HRPI	Telecon: B. Bollwage/G. Reis re: submission of 24-Month Rat Carcinogenicity Report this week & request for review by toxicologist as soon as possible upon receipt. Request acknowledged.
06/10/87	FDA/HRPI	Amend Sec. 9 to Protocols 350, 352 and 354.
06/15/87	FDA/HRPI	IND Safety Report. Project 179, Category 600 Investigator FCT, Patient 0021.
07/08/87	FDA/HRPI	Protocol Amendment: New Investigators #1. G. Neiss, MD, M. Varat, MD (Investigators) S. Spangenthal, MD, K. Musselman, MD (Co-Investigators) Protocols 354 & 201.
07/21/87	FDA/HRPI	Protocol Amendment: New Investigators #2. K. Adams, MD, R. Goldstein, MD-Investigators and J. Curtis, MD, D. Bradley, RN, H. Patterson, Pharm.D., D. Wohns, MD, J. jPalumbo, MD (Co-investigators).
07/27/87	FDA/HRPI	Information Amendment: Pharm/Tox #1. Pathology Working Group Report.
07/29/87	FDA/HRPI	Protocol Amendment: New Co-investigators #3. W. Herndon, Jr., MD, E. Landis, Jr., MD, W. Roberts, MD and D. Wise, MD. G. Niess, MD (Investigator) has already been submitted on April 14, 1987 (Protocol 354).
08/03/87	FDA/HRPI	Protocol Amendment: New Investigators #4. M. Davidov,MD (Inv.) & F. Becker,MD (Co-Inv) Protocol 351. R. Goldstein,MD (Inv.) & R. Bonilla,MD (Co-Inv) Protocol 350. S.Zellner, MD (Inv) & L. Veraja,MD(Co-Inv) Protocol 354
08/03/87	FDA/HRPI	IND Safety Report Follow-Up: Project 179, Category 600, Investigator FCT, Patient 0021
08/07/87	FDA/HRPI	Protocol Amendment - New Investigator #5. G. Neiss (Investigator) L. Brunetti, MD, L.

Date of Message	TO/FROM	Subject
08/07/87	FDA/HRPI	Fleishmen, MD, K, Tam,MD S. Kessel, MD., D. Layton, MD (Co-Inv's) Protocol 354.
08/12/87	FDA/HRPI	Request for Pre-NDA meeting.
08/19/87	FDA/HRPI	FDA SUBMISSION ON ENALAPRIL. PROJECT 179, PROTOCOL 352, INVESTIGATOR 107, PATIENT 0710
09/01/87	FDA/HRPI	Protocol Amendment: New Investigator #6 Add Co-Investigator J. Klein, Protocol 354.
09/03/87	FDA/HRPI	Telecon: G. Reis/D. Bucceri to schedule pre-NDA meeting (Oct. 5, 3:00 pm) per our 8/12 request.
09/16/87	FDA/HRPI	Telecon: B. Bollwage/G. Reis re: pre-NDA meeting.
09/18/87	FDA/HRPI	Telecon: B. Bollwage/G. Reis re: pre-NDA meeting (6 desk copies of our pre-NDA sub'm. forwarded 9/17, agreement to invite J.Skelly to meeting, confirmed date of 10/5/87 at 3:00 pm).
09/18/87	HRPI/FDA	Telecon: G. Reis/B. Bollwage re: recent enalapril ADR report submitted to this IND.
09/18/87	FDA/HRPI	Information Amendment: Pharmacology/Toxicology #001.
09/22/87	FDA/HRPI	Submitting an agenda for October 5 pre-NDA meeting #002.
10/13/87	FDA/HRPI	Minutes of pre-NDA meeting held 10/5/87.
11/12/87	FDA/HRPI	Protocol Amendment: New Investigator #003 Investigator R. Gatewood, Jr., MD Protocol 201
11/24/87	FDA/HRPI	IND Safety Report: Project 179, Category 600 Investigator FCT, Patients 0068, 0070, 0069.
12/02/87	FDA/HRPI	IND Safety Report: Project 179, Category 600 Investigator FCT, Patient 0073.
12/07/87	FDA/HRPI	Annual Progress Report - #004.
12/23/87	FDA/HRPI	IND Safety Follow-up Report. Project 179, Category 600, Investigator FCT, Patient 0073.
02/04/88	FDA/HRPI	Meeting Request - General Correspondence #008.
02/05/88	FDA/HRPI	Information Amend: Pharmacology/Toxicology

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02/05/88	FDA/HRPI	#007.
02/12/88	FDA/HRPI	Telecon: B. Bollwage/G. Reis to request she disregard our 2/4 request for a meetin (008) re: Protocol 104.
02/18/88	FDA/HRPI	Information Amendment: Pharmacology/Toxicology #009.
02/24/88	FDA/HRPI	Telecon: Dr. Stager/Dr. Chi re: follow-up of discussion at pre-NDA conf. schedule to be held at 2:00 on March 2.
03/04/88	FDA/HRPI	Follow-up meeting on statistical matters discussed at pre-NDA conference (Drs. Patel & Stager and Drs. Ng & Chi).
04/13/88	FDA/HRPI	Protocol Amendment: New Protocol #010. Protocol 301, Investigator S. Lewis, MD.
05/06/88	HRPI/FDA	Telecon: Dr. Korkowsky (FDA, C-R Div.)/Dr. I Patel re: Protocol 301 (3-month Rx CHF Study Exercise Capacity Evaluation).
05/11/88	HRPI/FDA	Teleconference: Dr. Karkowsky/B. Bollwage, Drs. Patel, Gordon, Bender, Vander Elst re: dose-response data using Protocol 301.
05/24/88	FDA/HRPI	Protocol Amendment: New Investigators #012 Investigators Carley, Hampsey, Jackson, Klancke, Moses & Schlamowitz - Protocol 301
06/01/88	FDA/HRPI	IND Safety Report: Project 179, Category 600 Investigator FCT, Patient 0034.
06/02/88	FDA/HRPI	Protocol Amendment: New Investigators #013 Investigators Bloomstein, Chandraratna, Hanovich, Hossack, Wolfel & Mohowald - Protocol 301.
06/08/88	FDA/HRPI	Protocol Amendment: New Investigators #014 Investigators Luckasen and O'Reilly Protocol 301
06/24/88	FDA/HRPI	Protocol Amendment: New Investigators - #015 Investigators Harris, Morledge & Pine - Protocol 301.
06/30/88	FDA/HRPI	Protocol Amendment - New Investigators - Serial No. 016 Investigators Humbert, Touchon and Young Protocol 301
07/13/88	FDA/HRPI	Protocol Amendment: New Investigators Investigators Lee, Seides, Molk, Ryan &

Date of Message	TO/FROM	Subject
07/13/88	FDA/HRPI	Wistran - Protocol 301.
07/25/88	FDA/HRPI	Protocol Amendment: New Investigators. Investigators Bennett & Zewller.
08/16/88	FDA/HRPI	Serial No. 019. Protocol Amendment: New Investigators. Inv. N. Madias, MD (replacing N. Canzanello, MD) for Preotocol 352. Investigators E. Haddock, MD, P. Kaihlanen, MD & D. Ruff, MD (protocol 301).
08/23/88	FDA/HRPI	Serial No. 020. Protocol Amendment: Change in Protocol - Amendment 301.2.
09/12/88	FDA/HRPI	IND Safety Report: Project 179, Category 600 Investigator FCT, Patient 0102.
09/30/88	FDA/HRPI	Protocol Amendment: New Investigator Investigator M. Heng, MD Protocol 301
10/07/88	HRPI/FDA	Telecon: Dr. Graham (Medical Off., C-R Div.) & D. Bucceri re: our Protocol 301 Study. Dr. Grahan asking if we have amended study per the 5/6 telecon w/Dr. Karkowsky.
10/13/88	FDA/HRPI	Protocol Amendment: New Investigator. New co-investigators: M. Rotman, MD (under Inv. W. Bennett, MD) & R. Woodruff, III, MD (under Inv. H. Moses, MD). Protocols 301 and 301.2.
10/24/88	FDA/HRPI	Protocol Amendment: New Investigator Investigator M. Varat, MD - Protocol 301.
10/27/88	FDA/HRPI	IND Safety Report: Project 179, Category 600 Investigator FCT, Patient 0107.
11/30/88	FDA/HRPI	Annual Progress Report - #026.
12/06/88	FDA/HRPI	Protocol Amendment: New Investigator. InvestigatorL. Reduto, MD - Protocol 301 Serial No. 027 .
12/28/88	FDA/HRPI	Protocol Amendment: New Co-Investigator. New Co-Investigator J. Eldridge, MD under Investigator B. Molk, MD (protocol 301).
01/23/89	FDA/HRPI	Protocol Amendment: Change in Protocol/New Investigator Investigator J. Somberg, MD, Protocol 301.1 Serial No. 029
01/30/89	FDA/HRPI	Protocol Amendment: New Co-Investigator. Serial No. 030 New Co-Investigator L. Makandura, MD under Investigator P.

Date of Message	TO/FROM	Subject
01/30/89	FDA/HRPI	Chandraratna, MD, Protocol 301.
02/09/89	FDA/HRPI	Protocol Amendment: New Investigator Additional study site for J. Somberg, MD under Protocol 301 Serial No. 031.
02/16/89	FDA/HRPI	Protocol Amendment: New Investigator Investigator K. Farag, MD Protocol 301 Serial No. 033
02/16/89	FDA/HRPI	Foreign Report No. 89 0033 T01M.
03/03/89	FDA/HRPI	Safety Follow-Up Report: Project 179, Category 600, Inv. FCT, Patient 0102.
03/06/89	FDA/HRPI	Protocol Amendment: New Investigator Adding Inv. C. Celano, MD along with T. Jackson, MD who was previously subm'd on 5/24/88 - Serial No. 035.
03/15/89	FDA/HRPI	Protocol Amendment: New Investigator Investigator G. Fletcher, MD to Protocol 301 Serial No. 036.
04/04/89	FDA/HRPI	Information Amendment: Pharmacology/Toxicology - Cross-referencing our 4/4/89 amendment to our IND - Serial No. 037.
04/07/89	FDA/HRPI	Protocol Amendment: New Investigator Submitting a revised Form 1572 changing the study site and deleting the subinvestigators in the submission dated 4/13/88. Serial No. 038.
04/25/89	FDA/HRPI	IND Safety Report: Project 179, Protocol 301 Inv. 167, Patient 0017/0508, Case Number 89 0226 T03M.
05/01/89	FDA/HRPI	Protocol Amendment: New Investigator. Inv. S. Sedlis, MD under Protocol 301. Serial 040.
05/22/89	FDA/HRPI	IND Information Report: Project 179, Prot. 301, Investigator 082, Patient 802/KC, Case No. 89 0290 T03M.
05/26/89	FDA/HRPI	Information Amendment: Clinical. Request for Review/Comment. Serial No. 042.
06/16/89	HRPI/FDA	Telecon: K. Bongiovanni (CSO)/B. Bollwage to schedule meeting w/HRPI to discuss the UK Mortality Trial with Drs. Temple, Lipicky, Bourke and a statistician.
07/06/89	FDA/HRPI	Foreign Case No. 89 0292 T01M.

Date of Message	TO/FROM	Subject
07/06/89	FDA/HRPI	General Correspondence. Letter confirming a meeting for July 12. Serial No. 044.
07/17/89	FDA/HRPI	Protocol Amendment: New Investigator. Investigator M. Wish, MD under Protocol 301. Serial No. 045.
07/21/89	FDA/HRPI	Protocol Amendment: New Investigator. Inv. T. LeJemtel, MD under Prot. 301. Serial No. 046.
08/23/89	FDA/HRPI	Protocol Amendment: New Investigator. Inv. W. Smith, MD under Protocols 301, 301.1 and 301.2. Serial No. 047.
09/08/89	FDA/HRPI	Protocol Amendment: New Investigator (sub). Adding subinvestigator L. Hendley, MD under principal investigators C. Celano, MD & T. Jackson, MD under Protocol 301. Serial #048.
09/19/89	FDA/HRPI	Foreign Case No. 89 0293 T01M.
10/02/89	FDA/HRPI	Protocol Amendment: New Investigator (sub). Subinvestigator N. Camba, MD under Principal Investigator J. Somberg, MD, Prot. 301. Serial No. 050.
10/11/89	FDA/HRPI	Protocol Amendment: New Investigator. Investigator A. Saenz, MD under Protocol 301 Serial No. 051.
10/20/89	FDA/HRPI	Foreign Case No. 89 0404 T01M.
10/24/89	FDA/HRPI	Protocol Amendment: New Investigator. Inv. R. Froelich, MD under Protocol 301. Serial No. 053.
12/14/89	FDA/HRPI	Annual Progress REport #054.
12/18/89	FDA/HRPI	Protocol Amendment: Change in Pro. 301.3/New Investigator. Adding subinv. Z. Boshra, MD under Prot. 301. Adding Inv's Itscoitz,Satin & Schwartz (Prot. 301, 301.3), Steiner (Prot 301, 301.2) and Sratmann (Prot. 301).
01/22/90	FDA/HRPI	Protocol Amendment: New Investigator. Adding subinv. F. Gravino, MD under principal inv. S. Itsoitz, MD (previously submitted) under Protocol 301. Adding Inv. S. Rosenblatt, MD under Prot. 301. Serial No. 056.
03/29/90	FDA/HRPI	Information Amendment: Clinical. Serial No. 058.

Date of Message	TO/FROM	Subject
04/06/90	FDA/HRPI	Protocol Amendment: New Investigator. Adding investigators D. Blecker, MD and S. Gupta, MD under Prot. 301. Serial #059.
04/06/90	HRPI/FDA	Summary of 7/12/89 meeting between HRPI, HAG and FDA re: Mortality Trial described in Amendment 042 dated 5/26/89 as requested by B. Bollwage on 4/3/90.
04/19/90	FDA/HRPI	Protocol Amendment: Change in Protocol (for the AIRE Study). Serial No. 060.
04/25/90	FDA/HRPI	Foreign Case No. 90 0067 P13M.
05/01/90	FDA/HRPI	Protocol Amendment: New Investigator (sub). Adding subinvestigator M. Reynolds, MD under Protocol 301.
06/04/90	FDA/HRPI	Foreign Case No. 89 0520 T01M.
06/25/90	FDA/HRPI	Foreign Case No. 89 0520 T01M (follow-up).
06/28/90	FDA/HRPI	Protocol Amendment: New Investigator. Inv. P. Mohanty, MD under Protocol 301. Serial No. 301.
07/03/90	FDA/HRPI	Foreign Case No. 90 0052 P13M.
07/10/90	FDA/HRPI	Foreign Case No. 90 0395 T01M.
07/12/90	FDA/HRPI	Protocol Amendment: Change in Study Site. Protocol Amendment: New Investigator. Changing D. Cassidy, MD from a subinvestigator to a co-principal investigator. Adding Inv. K. Jaobson, MD. Prot. 301. Serial #068.
07/18/90	FDA/HRPI	Letter to Compliance Officer at JFK Airport re: Notice of Detention giving the IND number and requesting that it be put on all invoices & FDA entry forms for future shipments of Ramipril powder from Frankfurt.
07/30/90	FDA/HRPI	Protocol Amendment: New Protocol (104). Information Amendment: C/M/C. Serial No. 069
08/06/90	FDA/HRPI	Foreign Case No. 90 0378 T03M.
08/20/90	FDA/HRPI	Protocol Amendment: New Investigator (sub). Adding subminv's N. Coutinho, MD & R. Singh, MD under previously subm'd Inv. J. Somberg, MD. Deleting J. Macioch, D.O. & M. Zevitz,MD as subinvs. previously subm'd (Protocol 301)
10/29/90	FDA/HRPI	Protocol Amendment: New Investigator. Inv.

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Date of Message	TO/FROM	Subject
10/29/90	FDA/HRPI	I. Eisenstein, MD under Prot. 301. Serial #074.
11/01/90	FDA/HRPI	Protocol Amendment: Change in Protocol. Modified Protocol 104 in accordance with comments from Drs. Teng, Huang & Hepp. Serial No. 075.
11/09/90	FDA/HRPI	Information Amendment: Clinical. Safety monitoring report for the AIRE study. Serial No. 076.
11/20/90	FDA/HRPI	Annual Progress Report No. 077.
12/14/90	FDA/HRPI	Foreign Case No. 90 0195 P13M.
03/05/91	FDA/HRPI	Information Amendment: Clinical. Safety monitoring report for the AIRE Study. Serial No. 079.

EXHIBIT E-2

Date of Message	TO/FROM	Subject
11/02/88	FDA/HRPI	Original NDA.
11/16/88	HRPI/FDA	Telecon: Dr. Bourke, Med. Off./B. Bollwage to ask several questions regarding the clinical reports in the NDA. We will call back on 11/21 to respond.
11/17/88	HRPI/FDA	Acknowledges receipt of NDA and assigns NDA No. 19-901.
11/23/88	FDA/HRPI	Teleconference: Drs. Patel & Gordon & B. Bollwage/Dr. R. Bourke to respond to his questions of 11/16/88.
11/23/88	HRPI/FDA	Telecon: Dr. Stuart Zimmerman has been assigned review responsibilities for Cardace & we can expect questions similar to those in Symcor review. Also, there may be problem w/name as there are 2 similar ones.
12/19/88	HRPI/FDA	Telecon: S. Zimmerman/D. Bucceri re: C/M/C review he did for IND (3/84).
12/21/88	FDA/HRPI	Telecon: B. Bollwage/Dr. Wolters re: his objections to trade name "Cardace."
01/12/89	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni to req. 90-day conference.
01/13/89	FDA/HRPI	Methods validation information (as discussed on 1/13) provided by Dr. Zimmerman for corrective action.
01/31/89	FDA/HRPI	Teleconference: B. Bollwage/N. Cappuccino, P. Okarma & S. Zimmerman to discuss C/M/C points raised in his draft review rec'd 1/20/89.
02/10/89	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni to request 90-day conference. She will check w/individual reviewers, make arrangements for a phone conference and call back in a week.
03/23/89	HRPI/FDA	Telecon: D. Segal/B. Bollwage to obtain information in preparing to perform inspections of our pivotal clinical trials (250, 253, 254, 350, 351, 354).
03/29/89	FDA/HRPI	Providing Protocols 250, 253, 254 and 350 & a list of investigators.
03/31/89	FDA/HRPi	120-day Safety Update.

Date of Message	TO/FROM	Subject
04/04/89	FDA/HRPI	Amendment to our NDA (toxicology studies).
04/07/89	HRPI/FDA	FDA considers our 4/4/89 amendment major & adds 90 days to review time. New due date is 8/5/89.
04/10/89	FDA/HRPI	NDA Supplement - C/M/C
04/14/89	FDA/HRPI	Telecon: Bollwage, Spiro, McCann/Dr. Graham to report death of patient in Protocol 301.
05/04/89	HRPI/FDA	Dr. R. Bourke's (Medical Officer) review of NDA and questions re: adverse reaction (cardiac arrhythmias, hypotension & cardiac death) discrepancies between NDA and our 120 day Safety Update.
05/05/89	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: Dr. Bourke's letter (5/4) explaining that it does not constitute final "approvable" decision.
05/12/89	FDA/HRPI	Telecon: Bollwage/Bongiovanni re: missing medical review pages and status of Biostat & Pharm review.
05/16/89	FDA/HRPI	Telecon: M. Gordon, C. Thayer, B. Bollwage/ Dr. Bourke to discuss Patient 802, a near sudden death patient in Protocol 301.
05/18/89	FDA/HRPI	Letter from Dr. Lipicky formalizing the 5/4 communication from Dr. Bourke w/recommendations & requests re: adverse reaction discrepancies between NDA and 120 day Safety Update.
06/23/89	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni. Meeting w/Temple, Lipicky and statistician has been scheduled for July 12 at 2 p.m. in Temple's conference room, 14B-45.
07/13/89	FDA/HRPI	Telecon: Bollwage/Rosenstock to R. Wolters re: trade name "Cardace."
07/28/89	FDA/HRPI	Telecon: D. Bucceri/K. Bongiovanni re status of NDA (currently listed for 12/89).
08/03/89	FDA/HRPI	Report of July 12 meeting at FDA w/HAG, HRPI and Prof. Ball from U. of Leeds.
08/16/89	HRPI/FDA	Telecon: K. Bongiovanni/B. Bollwage re: status of our response to clinical questions in Dr. Lipicky's 5/18 letter.

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08/30/89	HRPI/FDA	Telecon: Dr. Teng/B. Bollwage to request further information needed to continue biopharmaceutic review.
09/05/89	FDA/HRPI	Telecon: H. Lassman/Dr. Teng concerning her request for additional biopharmaceutics analytical data (Bollwage memo of 8/30).
09/07/89	FDA/HRPI	Response to FDA questions of May 18, 1989.
09/11/89	HRPI/FDA	Telecon: Dr. Bourke/Dr. Gordon to request detailed reports on each case of arrhythmia, hypotension & death (in the controlled trials only from the NDA).
09/13/89	FDA/HRPI	Telecon: Dr. Lassman/Dr. Teng & Dr. Eckert re: additional analytical data for various biopharmaceutics studies.
10/02/89	FDA/HRPI	NDA Amendment - C/M/C.
10/06/89	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni (CS) re status of reviews, including C/M/C Amendment submitted 10/02.
10/10/89	HRPI/FDA	Telecon: Dr. Teng/B. Bollwage re: biopharm review.
10/19/89	FDA/HRPI	NDA Amendment - Biopharmaceutics Data.
10/23/89	HRPI/FDA	FDA considers 10/19/89 amendment major and added 90 days to review time. New due date is 1/18/90.
11/09/89	HRPI/FDA	Letter: Dr. Stager/Dr. Hung requesting blood pressure data for Study 253 & 254.
11/17/89	FDA/HRPI	Teleconference: D. Huang, J. Sanocki and J. Zimmerman/Dr. Hung to clarify his request of Nov. 9 re: blood pressure data (Study 253 & 254).
11/22/89	FDA/HRPI	Amendment to an Unapproved Application (request by Dr. James Hung, Biometrics).
12/05/89	FDA/HRPI	Amendment to an Unapproved Application.
12/11/89	FDA/HRPI	Amendment to an Unapproved Application.
12/12/89	FDA/HRPI	Amendment to an Unapproved Applicaiton. Response to September, 1989 telephone inquiry.
12/15/89	FDA/HRPI	Telecon: M. Gordon/Dr. Bourke re: status of

Date of Message	TO/FROM	Subject
12/15/89	FDA/HRPI	information sent to him on 11/22.
12/15/89	FDA/HRPI	Teleocn: Dr. Gordon/Dr. Bourke to follow up on the status of a document he had requested last month.
12/18/89	FDA/HRPI	Amendment to an Unapproved Application (analytical data requested by Dr. Teng).
12/21/89	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: status of medical review and the individual reviews.
12/28/89	HRPI/FDA	Telecon: S. Zimmerman/B. Bollwage. Review of C/M/C Amendment dated 11/2/89 complete. He will send draft letter of his comments.
12/28/89	HRPI/FDA	Copy of draft letter from Dr. Lipicky following review of NDA with recommendations and requests for M/C portion.
01/05/90	HRPI/FDA	Medical Officer, Robert S. Bourke, MD Supplementary review.
01/11/90	FDA/HRPI	Telecon: Dr. Lassman/Dr. Ching Teng (Biopharmaceutics Div.) to determine status of review (will not get to it until late Feb. or early March).
01/12/90	FDA/HRPI	Telecon: J. Zimmerman/Dr. J. Hung/Biometrics to determine status of his review.
01/18/90	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: S. Zimmerman's C/M/C questions & Dr. Teng's being removed from Cardace review due to other priorities.
01/19/90	HRPI/FDA	Telecon: K. Bongiovanni/B. Bollwage re: diskettes for transmission of carcinogenicity data.
01/30/90	HRPI/FDA	Telecon: S. Zimmerman/B. Bollwage re: C/M/C, Methods Validation & Trade Name.
02/12/90	FDA/HRPI	NDA Supplement - C/M/C isomerism.
02/12/90	FDA/HRPI	Amendment to unapproved application - trade name survey.
02/14/90	FDA/HRPI	Confirmation of meeting on 2/22 at 9:00 with Drs. Wolters and Zimmerman re: isomerism.
02/26/90	FDA/HRPI	Amendment to an Unapproved Application. Submitting a diskette containing the carcin-

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02/26/90	FDA/HRPI	ogenicity data (hard copy also provided).
03/01/90	File	HRPI's Minutes of 2/22/90 meeting at FDA with Drs. Wolters & Zimmerman.
03/05/90	FDA/HRPI	Telecon: H. Lassman/Dr. Teng re: status of biopharmaceutics review.
03/07/90	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: review status. Dr. Fenischel expects to begin his review around the beginning of April.
03/15/90	FDA/HRPI	Teleconference: Bucceri/Bollwage/Dietel and Dr. Wolters re: use of trade name Carpril.
03/27/90	HRPI/FDA	Telecon: Dr. Ali/A. Schwink to clarify point in guidelines for computerization of carcinogenicity data.
04/30/90	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: status of NDA. Dr. Lipicky has targeted ramipril to leave C-R Division to go to Dr. Temple by the end of July.
05/01/90	FDA/HRPI	Telecon: H. Lassman/Dr. Teng re: status of her review (Biopharmaceutics).
05/16/90	FDA/HRPI	Amendment to an Unapproved Application. Methods Validation Package.
06/07/90	HRPI/FDA	Questions following review of our 11/2/88 & 3/31/89 submissions.
06/11/90	FDA/HRPI	Minutes of 6/7 meeting at FDA re: SBA.
06/12/90	FDA/HRPI	Teleconference: M. Gordon/Dr. Fenichel, who agreed to accept a copy of MS Word package to assist us in the SBA preparation.
06/14/90	FDA/HRPI	Telecon: J. Ostroff/Dr. Fenichel re: type of disk drives he has on his PC. Two software packages were sent to him on 6/20.
06/15/90	FDA/HRPI	Teleconference: Bucceri, Doerr, Lewis & Schwink/Dr. Resnick concerning statistical review of cardinogenicity data.
06/15/90	HRPI/FDA	Teleconference: Dr. Teng/H. Lassman to request additional assay validation data for her review of the biopharmaceutics section of the NDA.
06/19/90	FDA/HRPI	Telecon: D. Bucceri/K. Bongiovanni re: the

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06/19/90	FDA/HRPI	substance of our 6/14 telecon w/Dr. Resnick. She will brief Dr. Fenichel & send me a copy of the statistician's revised report.
06/19/90	FDA/HRPI	Copy of our understanding of the 6/14 telecon w/Dr. Resnick re: the Statistical Review and Evaluation, dated 4/12/90, of our rat & mouse carcinogenicity studies.
06/19/90	HRPI/FDA	Questions from statistician following review of our 11/7/88 & 2/28/90 submissions.
06/25/90	HRPI/FDA	Telecon: Dr. Teng/Dr. Lassman re: the GC urine method validation data she requested.
07/02/90	FDA/HRPI	Faxed correspondence from HRPI to Dr. Fenichel concerning a draft summary of the primary efficacy studies for the ramipril SBA.
07/05/90	FDA/HRPI	Submission of bioequivalence Protocol 104.
07/09/90	FDA/HRPI	Submission of Report #HOE 498/1/D/127 and Validation Data.
07/13/90	DRA/HRPI	Draft of the entire major clinical trials section of the ramipril SBA.
07/13/90	FDA/HRPI	Telecon: J. Hubbard/Dr. Teng re: her review of HOE 498/8/USA/104 -- bioequivalency study
07/18/90	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: Protocol 104.
07/18/90	FDA/HRPI	Correspondence from HRPI to Dr. Fenichel containing draft sections of the SBA.
07/18/90	FDA/HRPI	Teleconference: Bollwage, Bucceri, Chen, Hubbard, Lassman, Stager/Dr. Teng re: Prot. 104.
07/20/90	FDA/HRPI	Submission of bioequivalence Protocol 104 (revised).
07/23/90	FDA/HRPI	Correspondence from HRPI to Dr. Fenichel containing draft sections of the SBA.

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07/30/90	FDA/HRPI	Letter stating the new trade name: Altace (formerly Cardace).
07/30/90	FDA/HRPI	Correspondence from HRPI to Dr Fenichel containing a draft of the Animal Pharmacokinetics and Animal Pharmacology Secion of the SBA.
08/01/90	FDA/HRPI	Summary of July 31 meeting at FDA with Dr. Fenichel and Drs. Gordon & Vander Elst & D. Costello.
08/02/90	FDA/HRPI	Proposed draft package insert, draft SBA, draft clinical pharmacology section, listing of discontinuations from U.S. hypertension trials.
08/02/90	FDA/HRPI	Teleconference: D. Bucceri, B. Bollwage, B. Doerr, J. Lewis, A. Schwink/Dr. Resnick re: statistical review of our carcinogenicity amendment submitted July 25.
08/03/90	FDA/HRPI	Teleconference: D. Bucceri,H. Lassman,I.Ho/ Drs. Huang, Hepp & Teng to clarify the FDA position on various bioavailability/bioequivalence/pharmacokinetic studies.
08/10/90	HRPI/FDA	Telecon: Dr. Fenichel/M. Gordon re: testing the safety & efficacy in the pediatric population & the mouse carcinogenicity trial.
08/13/90	FDA/HRPI	Telecon: H. Lassman/Dr. Shah re: need for bioavailability/bioequivalency study for all dosage strengths when they were not proportional. Study HOE 498/Prot. 104 should be adequate along w/appropriate dissolution data.
08/14/90	HRPI/FDA	Telecon: K. Bongiovanni/B. Bollwage re: location of stat analyses of 24 mo. carcinogenicity study in NDA. She also confirmed receipt of pediatric survey form sent to Dr. Gordon.
08/15/90	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: submission of reanalysis of Prot. 350.
08/15/90	FDA/HRPI	Finalized draft SBA, draft package insert & the summaries of subjects discontinuing treatment for adverse reactions & Addendum to Protocol 350.
08/20/90	HRPI/FDA	Telecon: S. Zimmerman/B. Bollwage to inquire into the availability of samples for methods

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08/20/90	HRPI/FDA	validation testing. He has also submitted a request for a GMP check.
08/21/90	FDA/HRPI	Final report of a Pharmacokinetics Study HOE 498/1/GM/105.
08/22/90	FDA/HRPI	Samples of ramipril powder and 1.25 mg capsules sent to FDA labs in Los Angeles and St. Louis for methods validation per Dr. Stuart Zimmerman's request.
08/29/90	FDA/HRPI	Submitting a report in response to the Biopharmaceutics Division's comments of August 3, 1990.
08/29/90	HRPI/FDA	FDA letter by fax containing several requests re: Protocol 104.
08/29/90	HRPI/FDA	Letter containing several requests re: Prot. 104 previously faxed to us on 8/29.
08/31/90	HRPI/FDA	Telecon: J. Redd/B. Bollwage to advise that he did not receive a sample of Dibenzoyl Tartaric acid (LA District).
08/31/90	FDA/HRPI	Telecon: M. Gordon/Dr. Fenichel to discuss our proposal for conducting ramipril studies in pediatric subjects.
09/10/90	FDA/HRPI	Letter to Dr. Fenichel from M. Gordon in response to 8/31 discussion re: clinical trials to be conducted in pediatrics.
09/11/90	FDA/HRPI	Submitting a Phase IV progrm to investigate the safety and efficacy of ramipril in the young.
09/12/90	HRPI/FDA	Telecon: Dr. Fenichel/M. Gordon to discuss our position on the use of ramipril in pediatrics. The NDA package should go to Lipicky this month and probably to Temple in October.
09/13/90	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni for FDA input regarding the tox reports we have on hand. Dr. Reznick requested we submit as an NDA Amendment. He also requested summary tables & narrative summary.
09/13/90	FDA/HRPI	Telecon: H. Lassman/Dr. Teng in response to questions given to B. Bollwage by the CSO in Biopharmaceutics.
09/14/90	FDA/HRPI	Telecon: H. Lassman/Dr. Hepp re: report on

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11/16/90	FDA/HRPI	re: review priorities, etc. after it has been forwarded to Cardio-Renal.
11/20/90	HRPI/FDA	Telecon: H. Lassman/Dr. Hepp re: finalization of Protocol 104 bioequivalence to FDA by early next week.
11/27/90	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re: mtg. between Lipicky & Fenichel to go over final review package and types of postmarketing studies they would require.
11/28/90	FDA/HRPI	Amendment to an Unapproved Application. Submission of Protocol 104.
11/28/90	FDA/HRPI	Telecon: D. Bucceri/K. Bongiovanni to follow up on her conversation w/B. Bollwage re: final review package & postmarketing studies todefine the dose and dose interval further. Pkg. expected to go to Temple on 11/29.
12/07/90	FDA/HRPI	Telecons: 12/7 & 10 - H. Lassman/Dr. Hepp & Dr. Teng re: status of Biopharmaceutics review (Prot. 104).
12/12/90	HRPI/FDA	Questions raised by FDA following review of our NDA.
12/13/90	FDA/HRPI	Telecon: D. Bucceri/Dr. Teng to follow up on Dr. Lassman's 12/10 call. She is still working on the NDA & will discuss it tomorrow with her supervisor, Dr. Parkh.
12/14/90	FDA/HRPI	Telecon: D. Bucceri/Dr. Teng re: status of review. The "approvable" letter is in Dr. Temple's office but not on his action list because Biopharm review not complete. Drs. Teng/Parekh will be speaking w/Dr. Lipicky.
12/17/90	FDA/HRPI	Telecon: H. Lassman/Dr. Teng re: status of her review. She did not want to provide any information at this time but said to interpret "no news as being good news."
12/19/90	HRPI/FDA	Telecon: K. Bongiovanni/B. Bollwage to say that Dr. Lipicky is planning an Advisory Comm. meeting for March 1991 to examine approved & pending ACE inhibitors re: their defined dose range & dose interval.
12/21/90	FDA/HRPI	Final Safety Update.

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01/03/91	HRPI/FDA	FDA letter responding to our submissions to address the Form 483 issued following their 9/17/90 inspection.
01/04/91	FDA/HRPI	Telecon: D. Bucceri/K. Bongiovanni re: status of Drs. Fenichel & Temple's reviews (copy of PI w/Temple's handwritten comments fax'd to us attached).
01/07/91	HRPI/FDA	Copy of portion of memo Temple sent to the C-R Division which was faxed to M. Gordon by Dr. Fenichel.
01/07/91	HRPI/FDA	Copy of page 13 which was missing from the Package Insert transmitted to us last week.
01/08/91	FDA/HRPI	Telecon: B. Bollwage/K. Bongiovanni re FDA's 1/3 letter concerning the Form 483. Our Oct. 16 amendment is satisfactory & accepted by the C-R Division.
01/08/91	FDA/HRPI	Copy of the package insert incorporating Drs. Temple and Fenichel's revisions.
01/10/91	HRPI/FDA	Copy of SBA submitted 10/30/90 with comments from Dr. Temple and revisions by Drs. S. Zimmerman and R. Fenichel.
01/16/91	FDA/HRPI	Faxed copies of three cases requested by Dr. Fenichel (2 of which were sent in as IND safety reports).
01/17/91	FDA/HRPI	Teleconference: D. Bucceri, H. Lassman/K. Bongiovanni to respond to 2 questions posed earlier by Dr. Temple. They are drafting the approvable letter which they hope to bring to Temple this afternoon.
01/21/91	FDA/HRPI	Report on FDA meeting held January 18 re: ACE Inhibitors including remarks from Dr. Lipicky as to questions he intends to pose to the C-R Advisory Committee (mtg. tentatively scheduled for June).
01/23/91	HRPI/FDA	Telecon: K. Bongiovanni/D. Bucceri re: possibility of issuing an approval rather than an approvable letter (which would include commitments of the applicant as conditions of approval).
01/24/91	FDA/HRPI	Withdrawal of contract packager: PACO.
01/24/91	FDA/HRPI	Confirmation of HRPI's participation in the proposed Advisory Committee Meeting to re-

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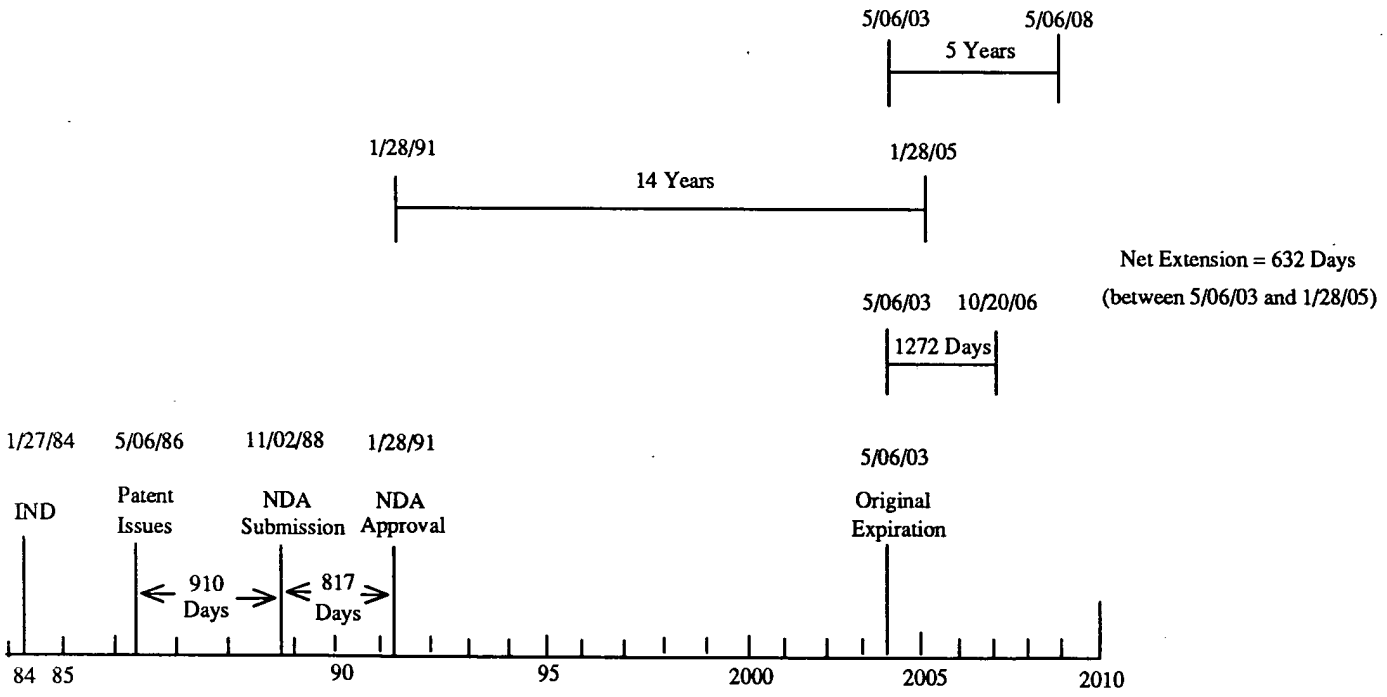
01/24/91	FDA/HRPI	view ACE inhibitors.
01/24/91	HRPI/FDA	Telecon: S. Zimmerman/D. Bucceri re: dropping the Paco (Pennsauken facility) from the NDA as a condition of approval as it had not been inspected for the desired dosage form.
01/25/91	HRPI/FDA	Telecon: K. Bongiovanni/D. Bucceri re: request for types of data each sponsor has to present at the ACEI Advisory Committee mtg. in June prior to scheduling a working meeting on 2/1 from 10 am to 12 noon.
01/28/91	HRPI/FDA	Faxed copy of APPROVAL LETTER and PI with revisions requested. Hard copy of letter to be Fed Ex'd today.


5/06/03
5/06/08
5 Years
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14 Years
Net Extension = 632 Days
(between 5/06/03 and 1/28/05)
5/06/03
10/20/06
1272 Days
1/27/84
5/06/86
11/02/88
1/28/91
5/06/03
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Patent Issues
NDA Submission
NDA Approval
Original Expiration
910 Days
817 Days
84
85
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EXHIBIT F